CLINICAL TRIALS IN SYSTEMIC LUPUS ERYTHEMATOSUS – THE DILEMMA. WHY HAVE PHASE III TRIALS FAILED TO CONFIRM THE PROMISING RESULTS OF PHASE II TRIALS?

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Abstract:

Systemic Lupus Erythematosus (SLE) is an autoimmune rheumatic disease of unknown etiology, characterized by the production of auto-antibodies and formation of immune complexes (IC) against self-antigens, and complement activation. This inflammatory response can lead to tissue infiltration and eventually, to organ damage.

Patients with SLE invariably have periods of relapse and remission. Flares can occur even when the patient is on seemingly adequate treatment, which suggests that more effective therapies are necessary for the management of SLE. Thus, trials with many drugs against different targets such as CD22, IL-12 and IL-23 or tyrosine kinases, have been carried out in recent years.

A frustrating feature of some of the biologic drugs used to treat SLE has been the reporting of successful phase II trials followed by failures of the phase III trials.

In this review we will focus on phase II and III trials carried out with epratuzumab (anti CD22), baricitinib (JAK inhibitor), rigerimod (P140 peptide) and ustekinumab (IL-12 and IL-23 inhibitor), and consider the reasons for their ultimate failure to 'make the grade'. Likewise, we will try to explain the possible reasons that can influence why good results may be obtained in phase II trials and lead to undue optimism.

Keywords:

Lupus, target, therapies, novel, monoclonals

CLINICAL TRIALS IN SYSTEMIC LUPUS ERYTHEMATOSUS – THE DILEMMA. WHY HAVE PHASE III TRIALS FAILED TO CONFIRM THE PROMISING RESULTS OF PHASE II TRIALS?

A frustrating feature of some of the biologic drugs used to treat systemic lupus erythematosus (SLE) has been the reporting of successful phase II trials followed by failures of the phase III trials. In this review we will focus on these drugs and consider the reasons for their ultimate failure to 'make the grade'. These reasons almost certainly include overly optimistic interpretation of phase II results, imbalance in the selection of patients between phase II and phase III trials, shorter duration of follow-up phase II trials and lower than expected placebo responses in phase II trials.

SLE is an autoimmune rheumatic disease of unknown etiology, characterized by the production of auto-antibodies and formation of immune complexes (IC) against self-antigens, and complement activation[1, 2]. SLE is thought primarily to be a B-cell mediated disease, characterised by polyclonal B cell hyper-reactivity[3]. These autoreactive B cells have a role in activating antigen presenting cells (APCs), producing inflammatory cytokines and regulating T cell activation and expansion[4]. This inflammatory response can lead to tissue infiltration and eventually, to organ damage[5].

Patients with SLE invariably have periods of relapse and remission. Flares can occur even when the patient is on seemingly adequate treatment, which suggests that more effective therapies are necessary for the management of SLE.

Approved treatments for SLE include hydroxychloroquine, corticosteroids and belimumab. Other immunosuppressants such as azathioprine, methotrexate, mycophenolate mofetil (MMF), ciclosporin, tacrolimus and cyclophosphamide, are also used in SLE patients[6]. To date, belimumab and anifrolumab are the only biological drugs licensed to be used in SLE[7-9] by the Federal Drug Administration (FDA), but biological agents are mainly used for patients with moderate and severe SLE. Voclosporin has also recently been aproved for the treatment of lupus nephritis (LN)[10]

The potential use of a monoclonal antibody to CD22, epratuzumab has also been explored[11-14]. Other targets of potential therapeutic value include anti-cytokine monoclonals and elsewhere TNF α blockers[15]. More recently, ustekinumab which blocks IL12 and IL23 has been tried in the treatment of non-renal lupus[16, 17].

Protein tyrosine kinases notably the Janus kinases (JAKs) or Tyrosine kinases (TKs) are expressed in several types of hematopoietic and immmune cells participating in both innate and adaptive immunity. They also have a role as mediators in the signalling of several proinflammatory cytokines, such as type l interferons, IL-6, IL-12 and IL-23; suggesting that they could be useful in the treatment of autoimmune diseases[18, 19]. Thus, trials with JAK inhibitors such as barcitinib[20], fenebrutinib[21] and other monoclonals to different targets implicated in differentiation and proliferation of B cells as CD40 ligand (CD40L)[22] have been carried out in recent years.

EPRATUZUMAB (antiCD22)

CD22 is a transmembrane sialoglycoprotein of the immunoglobulin family present specifically on B cells. It is implicated in regulation of B-cell function and survival[8, 23]. It contributed to the modulation of humoral immunity and also in the pathophysiology of B-cell lymphomas[24, 25].

Epratuzumab is a humanized antibody targeting the cell surface antigen CD22, regulating B cell signals and activation without a reduction in the number of B cells[8, 26]. Another effect of

epratuzumab is to inhibit the production of proinflammatory cytokines such as TNF-alpha and IL-6, without changes in the production of the antiinflammatory cytokines notably IL-10[26]. This results in the inhibition of B-cell activation, with the subsequent reduction of autoimmune and inflammatory events mediated by B-cells.

In early clinical trials, epratuzumab was found to be safe and effective in patients with non-Hodgkin lymphoma (NHL)[24, 25, 27] and in certain autoimmune diseases[27-29].

Thus, CD22 was considered a possible target to control the abormal B-cell function in SLE patients, and trials were duly carried out to try to demonstrate its efficacy.

THE PHASE II TRIALS

The first trial with Epratuzumab in SLE was published in 2006[11].

A total of 14 patients with moderate disease activity were included, all of whom received 360 mg/m^2 of epratuzumab every two weeks with a total of four doses. To asses the efficacy of treatment, British Isles Lupus Assessment Group (BILAG) index 2004 scores[30], were determined at 6, 10, 18 and 32 weeks. All patients experienced a clinical improvement, the BILAG score decreasing by 50% or more at some point during the period of study. It is important to mention that apart from this clinical improvement, a decrease in B-cell levels to around 35% at 18 weeks was noted and these levels remained low after 6 months of treatment. Encouragingly, no secondary infections or safety signals were reported.

Thus, this initial phase II trial demonstrated that four doses of 360 mg/m^2 of this monoclonal antibody were safe and well tolerated, leading to a clinical improvement in all patients for at least 12 weeks.

ALLEVIATE-1 and ALLEVIATE-2

ALLEVIATE-1 and ALLEVIATE-2[12], were two phase II-b double blind, placebo-crontrolled randomized trials looking at the efficacy and safety of epratuzumab in SLE. They included SLE patients with BILAG A disease activity affecting > 1 organ excluding renal and central nervous system (CNS), in ALLEVIATE-1; and BILAG B activity in > 2 organ systems in ALLEVIATE-2. Patients were randomized to different groups receiving placebo or epratuzumab in different dosage regimens. The response to the treatment was evaluated at week 12 and no significant difference in the BICLA response was found.

It is important to mention that ALLEVIATE 1 and 2, were discontinued prematurely (in September 2006) due to an interruption in medication supply (because of a manufacturing issue), so the primary endpoint had to be changed from the BICLA response at week 24 to week 12 so that some data from the trial could be analysed. 30.3% of the placebo group were BICLA responders compared to 44.1% of the patients treated with 360 mg/m2 of epratuzumab and 20% of those who received the higher dose (720 mg/m2) (p=0.177)[12]. It should be mentioned that corticosteroid sparing was found, and at week 24 the overall dose per patient was lower in the eprazutumab treated groups. A reduction of 1051 mg of prednisone (or equivalent) in the 360 mg/m2 group (p=0.03) and 1973 mg in the 720 mg/m2 group (p=0.08) was also observed, compared to placebo[31].

Thus, some of the analyses carried out in ALLEVIATE-1 and ALLEVIATE-2 provided support for the theory that treatment of SLE with epratuzumab at a dose of 360 mg/m2 added to standard of care (SOC) and corticosteroids might be an effective option to reduce and control SLE disease activity, and lower concomitant steroids.

EMBLEM

Wallace et al, published a phase II-b trial[13] that investigated the efficacy and safety of epratuzumab (in different doses) in moderate to severe SLE patients, with an Systemic Lupus Erythematosus Disease Activity Index 2000 K (SLEDAI-2K)[32] total score of 6 or more. The results were evaluated at week 12, and the primary endpoint was the responder rate according to a composite endpoint British Isles Lupus Assessment Group-based Composite Lupus Assessment (BICLA), that includes BILAG-2004[34], SLEDAI-2K[32], Physician Global Assessment (PGA) of disease activity[33] and no treatment failure.

227 patients were included, but 28 patients withdrew mainly due to lack of efficacy. At week 12, the responder rate in the placebo group (21.1%) was lower than in the epratuzumab groups (23.7-45.9%), but the overall treatment effect was not statistically significant (p=0.148)[13].

Several doses of epratuzumab were compared with placebo using the BICLA in this trial. The responder rates were greater in patients given epratuzumab compared to placebo. However, only those patients that received 2400mg CD [1200mg EOW/600mg weekly] reached statistical significance: The odds ratio (OR) for 600 mg weekly vs placebo was: 3.2 (95% CI 1.1-8.8 (p=0.03)) and OR for 1200 mg every other week (EOW) vs placebo: 2.6 (95% CI 0.9-7.1 (p=0.07))[13].

EMBODY-1 and EMBODY-2

Two phase III trials (EMBODY 1 and 2)[14], explored the efficacy and safety of epratuzumab in moderate to severe SLE. In these studies, patients were randomized into three groups: placebo, 600 mg epratuzumab weekly and 1200 mg epratuzumab every other week (EOW). The main objective was the BICLA responder rate at week 48 and secondary outcomes were the BICLA responder rate at weeks 12, 24 and 36, and corticosteroid changes from baseline to the dose at weeks 24 and 48.

793 patients in EMBODY-1 and 791 in EMBODY-2 were included. Of these patients, 265 (33.4%) and 258 (32.6%) withdrew prematurely from EMBODY 1 and 2 respectively. The most common cause of the discontinuation was lack of efficacy in all groups.

No significant difference comparing epratuzumab at either dose with placebo was found. In the EMBODY 1, BICLA response rates were 34.1% in the placebo therapy group, 39.8% in the epratuzumab at 1.200 mg EOW dose (p=0.175 versus placebo), and 37.5% in the epratuzumab 600 mg weekly dose group (p=0.442)[14]. With respect to EMBODY 2, BICLA response rates were 33.5% in the placebo arm, 34.1% in the epratuzumab 1.200 mg EOW group (p=0.899 compared to placebo), and 35.2% in the epratuzumab 600 mg weekly therapy group (p=0.716 compared to placebo)[14].

No significant differences in the secondary objectives were achieved including the corticosteroid sparing. Immunologically, results were comparable to the EMBLEM and ALLEVIATE trials, with a reduction of 30-40% in peripheral B cells noted in those patients who received epratuzumab which was not seen in patients given the placebo group. T cells, IgA and IgG levels were stable throughout the studies. In contrast, IgM levels decreased by 20% from baseline in epratuzumab-treated patients but the incidence of adverse events was comparable to the placebo group[14].

A post-hoc analysis [34] reported that SLE patients with an accompanying Sjögren's, but not those without SS, a higher proportion of patients receiving epratuzumab achieved a BICLA response and a reduction from baseline in BILAG score. These data do not seem to have been enough to convince the manufacturers to continue exploring the use of the drug.

BARICITINIB (JAK inhibitor)

Baricitinib is a selective and reversible inhibitor of JAK1 and JAK2 that mediates the signalling of numerous proinflammatory cytokines[35]. The success of using Baracitinib in rheumatoid arthritis where it clearly does reduce sinovitis [36] did encourage studies in SLE. A phase II trial of baricitinib [20] (2 mg or 4 mg, once-daily) in patients with active SLE explored the proportion of patients achieving resolution of manifestations notably arthritis or rash at week 24 as defined by SLEDAI-2K. The SLE Responder Index-4 (SRI-4)[37] response at week 24 was a secondary objective.

The 314 patients included were randomly assigned to one of three groups: placebo, baricitinib 2 mg/dy or baricitinib 4 mg/dy. 255 (81%) completed the 24-week study period.

The primary outcome was achieved with significantly more patients in the baricitinib 4 mg group (67%) than in the placebo group (53%) (OR 1.8, 95% CI 1.0-3.3; p=0.0414). It was achieved in 58% of the baricitinib 2 mg/dy group, however it did not reach statistically significant (OR 1.3, 95% CI 0.7-2.3; p=0.39)[20]. The proportion of patients who achieved an SRI-4 response at week 24 was also higher in the baricitinib 4 mg/dy group (64%) than in the placebo group (OR 2.0, 95% CI 1.2–3-6; p=0.0151) [25]. Patients receiving baricitinib 2 mg (51%), did not reach significance (OR 1.3, 95% CI 0.7–2.2; p=0.44)[20].

With respect to serious infections, they were noted in the baricitinib 4 mg group (6% patients) than in the 2 mg group or placebo group (1%).

Thus treatment with baricitinib 4 mg once-daily in addition to SOC therapy, was associated with significant clinical improvement compared to placebo. These results lead to a two phase III trial (SLE-BRAVE I and II)[38] but this was discontinued due to an absence of improvement in the group given baracitinib vs placebo. Interestingly, SLE-BRAVE-I showed a significant reduction in lupus disease activity (assessed by SRI-4) but the SLE-BRAVE-II trial did not. As the trials were discontinued, preliminary results were given but no figures or more specific data have yet been provided. The company is currently working to conclude the phase III SLE long-term extension trial (SLE BRAVE-X), designed to evaluate the long-term safety and efficacy of Baricitinib over three years in adults who completed SLE-BRAVE-I or II.

It is worth mentioning that safety was consistent with previous data on the drug and safety issues were not the reason to discontinue these trials.

RIGERIMOD (P140 peptide)

P140 peptide is a 21-mer linear peptide which comes from the small nuclear ribonucleoprotein U1-70K[39]. It is phosphorylated at the Ser140 position and it is recognized by both CD4+ T cells and antibodies from MRL/lpr mice[42, 43]. In prior studies with MRL/lpr lupus-prone mice model, it was shown that a P140 peptide reduced proteinuria, vasculitis and dermatitis and prevents production of antibodies to dsDNA in those MRL/lpr mice[40, 41]. These results encouraged the theory that a P140 peptide could be another option of treatment for SLE.

A phase IIb open-label study of 204 patients with moderately active SLE was undertaken [42]. These patients were treated with a low dose (200 of µg) of Lupuzor (Rigerimod) in different treatment regimens, plus SOC. 204 patients were randomly distributed: 68 patients for each treatment group. Patients of group 1 received 200 µg every 4 weeks; Group 2, Lupuzor 200 µg every 2 weeks and group 3 received placebo.

53.1% of patients in group 1 ($p<0.05$), 45.1% in group 2 ($p=0.18$) compared to 36.2% in group 3 (placebo arm) achieved an SRI response at week 12. At week 24, 59.2% in group 1, 58.8% in group 2

and 53.1% of the third group, achieved an SRI response; these results were not statistically significant[42].

These findings of this study showed that administration of 200 μg Lupuzor every 4 weeks, reduced disease activity in patients with moderate-severe SLE actitivity, who were receiving SOC.

A phase III trial that included 202 SLE patients was then performed[43]. Although a superior response rate in the rigerimod group over placebo was noted, this difference was not statistically significant (52.5% vs 44.6%, p=0.2631). In patients who had high anti-dsDNA autoantibodies at the start of the trial, a greater response rate over placebo (61.5% vs 47.3%, p = 0.0967) was noted, although this too was not statistically significant[43].

The company expressed their "disappointment" that the response rates of patients receiving rigerimod had not reached statistical significance compared to placebo. They manifested their trust in the investigational treatment as a potential therapy to bring a safe treatment to the Lupus patients, highlighting its safety profile, with no serious adverse events reported.

Therefore, they launched an open label phase III trial that is currently ongoing, and it is expected to reveal data in due course.

USTEKINUMAB (IL-12 and IL-23 inhibitor)

Ustekinumab is a human monoclonal antibody directed at the p40 subunit present in the cytokines IL-12 and IL-23[44], that has previously been approved for the treatment of psoriatic arthritis[45, 46] and Crohn's disease[47] in adults. As these cytokines are implicated in SLE pathophysiology, it was postulated that this could be a therapeutic agent in SLE patients.

PHASE II TRIAL

This trial[16] had as its primary endpoint the proportion of patients who achieved an SRI-4 composite response at week 24. Other secondary endpoints were the change from baseline in SLEDAI-2K and in PGA, and the proportion of patients with a BICLA response; at week 24.

In this trial, SLE patients with one BILAG-2004 domain A (severe manifestation) or two BILAG domain B (moderate manifestation) organ domain scores during screening, or both were included. They also had to have an SLEDAI-2K score of at least 6 during screening and a SLEDAI-2K score of at least 4 for clinical features despite optimal background treatment.

A total of 166 patients were included, of whom 102 were randomly assigned to receive placebo (n=42) or ustekinumab (n=60) in addition to the SOC therapy. During the period of the study, 13 patients (nine in the placebo group and four in the ustekinumab group) discontinued the study treatment, mainly due to adverse events (seven patients). One patient in the placebo group discontinued because of lack of therapeutic effect.

At week 24, a higher proportion of patients in the ustekinumab group achieved the primary endpoint of SRI-4 response than in the placebo group (62% in the ustekinumab group vs 33% in the placebo group; p=0.006)[16]. Patients in the ustekinumab group had a greater change in SLEDAI-2K score at week 24 than those in the placebo group (-4.4 [SD 2.9] vs –3.8 [SD 5.4] respectively; p=0.093[16]. The proportion of patients that achieved BICLA response at week 24, was similar in both groups; however the proportion of patients with no worsening in BILAG-2004 score was higher in the ustekinumab group compared to those that received placebo (48% vs 26% respectively; p=0.028)[16]. The BICLA response was not statistically different between the groups. These data led to the development of a phase III trial.

PHASE III TRIAL (LOTUS)

In this study[17], the inclusion criteria were the same as in the phase II.

1029 patients were enrolled of whom, 516 were randomized. Of those, 308 received ustekinumab (6 mg/kg intravenous at Week 0, followed by subcutaneous injections of 90 mg at Week 8 and every 8 weeks) and the other 208, placebo (intravenous at Week 0 and by subcutaneous injections at Week 8 and every 8 weeks thereafter). The period of study was 52 weeks. 258 patients withdrew from the trial by week 52. The main reason was that the study was discontinuated by the sponsor.

Unfortunately, the primary and secondary endpoints were not achieved: 44% of patients in the ustekinumab group and 56% of patients in the placebo group had an SRI-4 response at week 52 and during the study, 28% of patients in the ustekinumab group and 32% of patients in the placebo group had a BILAG flare[17]. Thus, there was no evidence that ustekinumab was improving the signs and symptoms of active SLE in the LOTUS population[17].

Neither primary and secondary endpoints were achieved in the overall population nor in any subpopulations. Thus, given these results, there is insufficient evidence to support the use of ustekinumab as an effective therapeutic alternative for SLE patients.

DISCUSSION

In contrast to the many successes in the biologic treatment of patients with rheumatoid arthritis, psoriatic arthritis and ankylosing spondylitis, biologic therapies for lupus clearly lag many years behind. Recent successes with Anifrolumab in non-renal lupus [48] and Voclosporin [49] and Benlysta [50] in renal lupus have given more room for hope. However, a particularly frustrating aspect of clinical trial development in lupus is the focus of this review, namely why is it that some biologic drugs eg. epratuzumab, baracitinib, lupuzor and ustekinumab, successful to some extent in phase II trials, then fail to meet their endpoints in phase III.

One possible explanation for this could be that companies have overinterpreted the positive signs coming from phase II trials encouraging them to proceed to a phase III, when a more detailed analysis indicates that such success as was achieved in the phase II trials was modest and probably unlikely to be observed in a phase III trial. The results observed in trials with epratuzumab or ustekinumab trials are an example of this. Thus, in EMBLEM phase IIb trial with epratuzumab an SRI response rate of 45.9% in the epratuzumab group given 2400 mg CD was noted vs 21.1% in the placebo group. This promising response observed in the epratuzumab group, added to the unusually poor response obtained in the placebo group in EMBLEM (21.1%) and in ALLEVIATE 1 and 2 (30.3%) trials, led to postulating epratuzumab would be a good therapeutic alternative and led to the consequent phase III trial. A higher SRI response rate was also observed in patients that received epratuzumab in phase the III trial, but this difference was not significant. Assesing ustekinumab, the SRI response rate was greater in the phase II trial (62% vs 33% compared to placebo) but this promising result was not confirmed in the later phase III trial, where an SRI responder rate was 44% in ustekinumab group and 56% in placebo arm.

In addition, baseline imbalance needs to be taken into account when interpreting the results, as occured for example in the ustekinumab trial. It may be that smaller (and shorter) phase II trials tend to capture more homogenous patient populations (within the highly heterogenous SLE population). In the phase II study, the proportion of patients with severe disease activity (≥1 BILAG A domain) was higher in the placebo group (52%) than in the ustekinumab group (45%), while in the phase III (LOTUS), BILAG A manifestations were more common in the ustekinumab group. Selection bias like

this, could explain why the placebo response rate was lower in the ustekinumab (placebo responder rate 33%) and epratuzumab (placebo respoder rate 21%) phase II trials, in contrast to phase III, where as above the placebo responder rates were 56% and 33.5% respectively. Discordant BICLAR/SRI results in the phase II trial should have been a warning signal to be heeded before moving to the phase III trial. As the placebo response increases, it becomes more difficult for a trial to achieve significant results and for the trial drug to be recognised as beneficial.

Differences in the rates of discontinuation from trials, may influence in the discordant results obtained between phase II and phase III. Thus, in the ustekinumab trial, 12.7% of patients discontinued phase II trial; while 50% of patients discontinued the phase III trial before week 52. A greater rate of discontinuation was also noted in the epratuzumab trials: 12.3% discontinued phase II trial and 33.4% and 32.6% phase III (EMBODY-1 and EMBODY-2 respectively). With respect to epratuzumab, this high rate of discontinuation could be secondary to the fact that in the phase III trial, patients were given the possiblity of enrolling in the open-label extension study if they withdrew at week 16 or later due to lack of efficacy, which might have motivated them to drop out. Better results might thus be apparent as a result of having the possibility of changing to another therapeutic group in the trial extension. Clearly a more detailed assessment of why patients drop out of phase II as opposed to phase III trials is warranted.

The shorter duration and the smaller sample size of phase II trials, might also be a limitation when interpretating results, since this could favorably influence some of the groups and also overestimate results observed in these trials. An example of this phenomenon was seen in ALLEVIATE-1 and 2 phase IIb trials, that included 90 patients. At week 12, 44.1% patients of patients who had received 360 mg/m^2 of epratuzumab and 20% of patients on 720 mg/m^2, met the primary endpoint while in the placebo group, it was 30.3% (p=0.177). Phase III trials (EMBODY-1 and 2), were longer (48 weeks) and included a greater number of SLE patients (n = 1257) and a slightly higher percentage of patients in the epratuzumab groups (37.5% in 600 mg/weekly arm and 39.8% in 1200 mg EOW group) met the primary objective vs 34.1% in placebo group, but these results were non significant. Thus, a longer treatment period and a greater number of patients, seems necessary to obtain more realistic results to avoid drawing prematurely optimistic conclusions in favor of a given therapy.

The high placebo response rate that was seen in many phase III trials is notable eg. those with ustekinumab (LOTUS) and rigerimod, probably reflects the fact that over time combinations of steroids and immunosuppression can achieve a reasonable degree of remission in many patients.

It can be argued that any clinical trial needs to pay close attention to ensuring that its investigators are fully trained to distinguish activity (including flare) from damage and concomittant disease in SLE trials. Where appropriate a renal biopsy and skin score (e.g. CLASI[51]). Clearly as we have discussed in this reivew, too many Phase III trials have not taken all of these factors into account. Perhaps the development of the equivalent to the ACR 20/50/70 in rheumatic arthritis might be worth developing. Although we will not describe the reports in great detail, it is important to reflect whether the recent successful trials in lupus with Benlysta, Anifrolumab and Voclosporin met these ‘ideas’.

In TULIP-1 and TULIP-2[48], it was shown that anifrolumab treatment at week 52 improved SLE disease activity compared to placebo, in many organ domains such as the musculoskeletal (56% vs 44% BILAG-2004, p=0.0025 and 49% vs 40% with SLEDAI-2K, p=0.025)[48] and mucocutaneous system (54% vs 38% with BILAG-2004, p=0.0001 and 55% vs 39% with SLEDAI-2K, p=0.0001)[48]. Importantly, in those patients with a CLASI-A of 10 or more at baseline, greater proportions of patients treated with anifrolumab achieved a CLASI-A response at week 12 compared to placebo

(46% vs 25%, p=0.0015)[48]; and this effect was mantained over the period of study. Thus, it was shown that patients treated with anifrolumab had higher rates of responder rates in SLE disease activity in the most frequently affected organs.Voclosporin was compared to placebo in SLE patients with active LN in another phase III trial[49]. A complete renal response at 52 weeks was achieved in significantly more patients in the voclosporin group than in the placebo group (41% vs 23%; p<0.0001).The phase III trial whose primary endpoint was to assess the efficacy of Belimumab in LN[50], showed that significantly more patients that received belimumab had a primary efficacy renal response 43% vs 32%; p=0.03), and also complete renal response (30% vs. 20%; p=0.02) at week 104, compared to those who received placebo.

Thus, in these phase III studies a greater number of patients were included (357 in Voclosporin trial[49], 448 in Belimumab[50] and 726 patients in Anifrolumab (TULIP-1 and TULIP-2)[49]) and a longer follow-up was also carried out (from 52[48, 49] to 104 weeks[50]), with favorable results.

Despite the fact that the phase III trials of the drugs included in this review recruited a larger number of patients and had a longer follow-up than those of phase II, the results obtained were not as successful as those obtained in the recent trials carried out with Voclosporid, Anifrolumab or Belimumab as it was mentioned above. This would support the idea that perhaps the sample of patients in the phase II trials was not representative, since the percentage of patients who responded in the placebo group was much lower than the percentage in the phase III trials; thus overestimating the effect in favor of the study drug.

In summary, it is clear that great attention to detail must be paid when assessing the seeming success of phase II trials in SLE. In particular placebo response rates below say 30%, short duration of follow-up and small numbers of patients studies may lead to undue optimism.

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